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## ANÆSTHESIA FROM COMMERCIAL ETHER- ADMINISTRATION AND WHAT IT IS DUE TO

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EVER since William Long in 1842, and Crawford in 1846, used a sample of so-called ether for anæsthesia, the medical profession have believed that this anæsthesia obtained, was due to ethyl ether. They have continued to use ether (supplied by commercial firms), and you will most likely agree with the statement that the ether as so supplied is at present considered to be the safest and best anæsthetic known. No doubt, but that every anæsthetist has at times mentally criticized the anæsthetic powers of certain cans or makes of ether, and on account of there being no apparent chemical reason, has laid the blame at the door of the patient. But there is a reason, a most vital reason, (other than idiosyncrasy), and that is that ether, ethyl ether, with which we are so familiar, is not an anæsthetic, and the analgesia which comes from the administration of commercial ether, is not due to ether, but rather to the impurities occurring in it.

The research leading up to these radical conclusions was started in the spring of 1915, when Dr. McKicken, of the Toronto General Hospital staff, observed that certain cans of ether emitted an unusual odour, the cause of which was considered worth looking into. Through the kindness of Dr. C. K. Clarke, Professor Hunter, and Dr. Samuel Johnston, we were enabled to undertake the investigation of commercial ethers in the laboratories of pathological chemistry. The various states of the chemical part were carefully checked by clinical observation of the different derivatives

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Preliminary paper and demonstration as given before the Canadian Medical Association in June, 1917.

recovered, and it was slowly recognized that some were irritative, some anæsthetic, and some toxic.

#### IRRITATIVE IMPURITIES

Concerning impurities causing irritation, these may be anterior nasal and due to alcohols or acetones; or nasopharyngeal and bronchial due to aldehydes. Aldehydes irritate, causing mucous in an ether dilution of less than '1 per cent. and it is possible that they may have something to do with ether pneumonia. The objectionable and often irritating odours of commercial ethers are due mainly to organic acids.

#### ANÆSTHETIC DERIVATIVES

Let us now consider anæsthesia proper. The substances derived, may be divided into two classes:

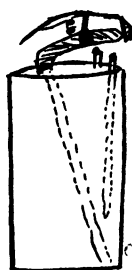
First. Narcotics (producing peripheral congestion and drunkenness);

Second. Analgesics (producing loss of sensation and peripheral vaso-motor spasm).

Absolute di-ethyl ether as has already been stated will not anæsthetize. Its administration produces peripheral congestion, and drunkenness. Prolonged administration causes muscular tremor, shortness of breath with expiratory grunt, a terrible sensation of impending danger, and increased congestion. As much as twenty ounces have been administered to one patient with only this effect. If, however, a small amount of carbon-dioxide be present, the peripheral congestion is relieved, and the patient enters the natural anæsthetic and analgesic stages. In order, therefore, to obtain anæsthesia proper, we must have acting a narcotic such as di-ethyl ether, together with an analgesic such as carbon-dioxide.

The carbon-dioxide-absolute-ether anæsthesia constitutes a type of its own. In a previous paper, read at the Academy of Medicine in Toronto, I compared the action of absolute ether to that of nitrous oxide, with which the carbon-dioxide tension factor is also a necessity. The anæsthesia produced by this carbon-dioxide-ether method is very similar to that obtained from nitrous oxide, and the recovery almost as rapid. It is of interest that Hickman, as early as 1828, used carbon-dioxide alone as an analgesic. Of course, in cases suffering from certain metabolic disorders it is contraindicated.

In practice it was found convenient to administer the carbondioxide in solution with ether. In order to do this, a can capable of acting like a syphon-soda bottle was used (such as shown in the diagram), the carbon-dioxide being injected into the ether under high pressure.



So far, only one narcotic in commercial ether has been dealt with, namely, di-ethyl ether. Other narcotic substances occurring in commercial ether and acting the same as di-ethyl ether, are:

- |   |   |
|---|---|
| 1. Alcohol—2 to 5 per cent.               |   |
| 2. Di-methyl ether (almost to saturation) | } Only in ethers<br>made from methy-<br>lated alcohols. |
| 3. Methyl-ethyl ether (a trace)           |   |
| 4. Methyl-propyl ether (a trace)?         |   |

These substances are all of a powerful narcotic aid. The last two—methyl-ethyl, and methyl-propyl ether—are very difficult to detect by odour as you will find by the samples, but the first two are easily differentiated.

But, of our ethers on the market, only a few contain carbon-dioxide in sufficient quantities to be of use, and therefore a further analgesic substance besides carbon-dioxide was looked for.

Absolute di-ethyl ether on being passed through a certain process was found to develop remarkable analgesic properties. With it almost major operations were performed with the patient still able to articulate clearly, without pain, and not at all sleepy. Its odour was found to be slightly sweeter than that of ordinary pure ether. It was the stage-acting of this substance that informed us there was something yet to learn concerning ether anæsthesia. The results obtained were so peculiar that men refused to believe them even on the word of our highest medical authorities unless they were witnesses. The symptoms were carefully studied in over two hundred cases. One case of special interest had administered to it in one month twenty-six such anæsthetics, as well as one nitrous oxide, one ether, and one ethyl-chloride. The duration of each administration was from fifteen to thirty minutes. With each of the old anæsthetics the patient was violently ill for some hours, but at no time after the analgesic ether was she to the slightest extent nauseated, even though she had had a meal immediately before. A description given by the patient of her sensations comes as near as possible to the truth:

"After a few breaths of a peculiar substance reminding me slightly of ether, but not so strong, I began to breathe heavily

and quickly, and was conscious of a feeling of exhilaration and excitement all over me. My heart seemed to beat faster, and I felt myself growing hot, especially in the face. Next my legs seemed to go around in a circular motion, and the sensation would spread through my whole body, although at no time did I feel in the least dizzy. At this stage, the dressing began and I could feel water being poured upon my fingers and always knew whether it was hot or cold. The bandages often seemed to stick on being removed but there was no pain. Sometimes when they seemed to be probing or cutting there was a pricking sensation. Dr. Cleland at this period would usually ask if it hurt, and my answer was either "a little" or "not yet". If I said "a little", more of the analgesic seemed to be administered for at this point I usually went completely under its influence, and neither felt the dressing or knew in any way what was going on; although as a rule if one of the doctors spoke to the other, I heard it and made some comment, almost always remembering afterwards what had been said.

"The effect of coming out of this anæsthetic, I can compare to being awakened suddenly from sleep. I do not know how it appeared to onlookers, but I felt as if I regained consciousness instantly. I could at once see, feel, and hear in a perfectly natural manner, and my brain was quite clear. There was one marked peculiarity. For several minutes after becoming conscious, I talked steadily in a slow disjointed way, pronouncing every syllable separately; and I voiced any and every idea that came into my head, exactly as a child does. In fact I seemed to be on the intellectual level of a child of about ten years old, and I must have caused much amusement. I was quite aware of all this at the time but seemed powerless to do otherwise. I sometimes felt a slight oppression in breathing, due to the odour lingering in the room, and would ask the windows to be raised; but there was absolutely no discomfort in any way recovering consciousness, rather a feeling of pleasurable stimulation.

"Several times when only a little was given me, I felt the same sensation which I have described—rapid breathing, accelerated heart action, heat, and excitement, but there the effect stopped, and I remained conscious throughout the dressing, feeling quite normal, neither childish nor talkative, but having absolutely no pain."

Careful concentration and extraction of gases from this analgesia product showed the presence of a gas with similar properties to that of ethylene ( $\text{CH}_2\text{-CH}_2$ ) (and another gas as yet not syn-

thetized). This ethylene, as it was not present in the absolute ether base, must have developed in the process. Ethylene was then manufactured, and added to absolute ether, and a similar analgesic product to that already described was obtained. It is therefore reasonable to believe that ethylene is at least one of the analgesic substances for which we were looking. The method for manufacturing ethylene was through the interaction of alcohol and sulphuric acid. The gas was found to be more efficient if made at  $175^{\circ}$  (rather than  $160^{\circ}$  C.). All dangers of production of carbon-monoxide were eliminated by blood testing. In order that an ether-ethylene solution will demonstrate the described properties, the ether to which the ethylene is added must be absolute. The reason this secret of ether anæsthesia has not been discovered before, is that processes to obtain pure ether have never been before originated. Analyses of every ether on the market shows traces of ethylene, and it is its concentration upon which the anæsthetic power of a said ether depends. If, for instance, it is present in sufficient quantity in a sample of ether, it is possible to have the patient lose all sensation before being made drunk by the narcotic solvents. That is, it is now possible with this knowledge to control sensation as well as narcosis. The state of drunkenness which is necessary for a certain grade of analgesia depends entirely upon the condition of the circulation of the patient.

A word here on administration of the ether-ethylene solution may save many from failure. We all recognize in commercial ether anæsthesia, that there is an exciting stage occurring previous to unconsciousness. When, as it is now possible, we can control sensation through ethylene concentration, the question arises, are we going to run analgesia, this, or the other side of the excitement stage. It is very annoying indeed to both surgeon and anæsthetist to decide on a pure analgesia this side of the excitement stage, and not to use a sufficiently concentrated gas-ether. Under such circumstances, the patient may state that they are entirely without feeling, but when major stimulation comes, they may squirm. If now the anæsthetist, instead of using another sample in which the gas is more concentrated, makes the mistake of trying to continue his too dilute gas-ether, the patient is going to enter the ordinary ether excitement stages, while being operated on.

When the anæsthetic stage is deeper than the excitement stage occurring with concentrated gas-ether, the patient is a very long time recovering sensation and reflexes. It is therefore of use in tonsil work.

It is worth bearing in mind that ethylene produced by alcohol sulphuric interaction is not quite absolute and therefore it is possible in the gas-ether described to have yet other analgesic factors besides ethylene. I have already mentioned that in the process-analgesic-ether, there are other gases which develop besides ethylene.

#### SOME FACTS BEARING ON PRIMARY ANÆSTHESIA

Discussion of our adopted theories and classifications from a physiological standpoint leads us to the tormenting problem of what anæsthesia really is. Professor Alexander McPhedran drew our attention at the Academy of Medicine to the fact that analgesia may be brought about in some cases by making them take a number of deep rapid respirations. A peculiar coincidence probably relative to this, is that the so-called analgesic substances, carbon-dioxide, ethylene, and other ether gases, when present in an ether, cause rapid, deep respirations much sooner than would occur otherwise.

The following experiments were carried out on myself and then checked by ten other cases with similar results.

Thirty deep inspirations were rapidly taken. No change of sensation resulted except a fullness in the head. One half-hour was allowed to intervene, and six to eight full breaths of analgesic ether were then taken slowly. No change of sensation resulted. Fifteen deep rapid breaths of pure air were immediately taken. Almost a complete loss of peripheral sensation followed. Normal breathing restored, while further rapid breathing again reduced it. With myself I was able to eliminate sensation three times in succession with the one dose of analgesic ether by this rapid breathing method.

It is very difficult indeed to imagine an explanation for the above phenomenon, or even to state whether it is a nerve or circulation condition which makes it possible. In one case who had six anæsthetics of analgesic ether there happened to be a large area of granulation tissue exposed. The absolute analgesic stage would start about forty-five seconds after the beginning of deep rapid respirations. At exactly the same time as the loss of sensation occurred in each administration, the granulation tissue blanched but there was no apparent blanching in the skin, or lips, or change in the pulse rate. Unfortunately the blood pressure in this case was not followed. More circumstantial evidence of perhaps some importance is that at the beginning of an ordinary ether anæsthetic,

the blood pressure usually rises, while later at the respiratory stimulation stage, it rapidly drops to some points below normal.

From the above facts it might be possible to theorize tentatively that ether anaesthesia is in part responsible to a relation to a certain condition of the peripheral circulation relative to the nerve endings.

#### POST OPERATIVE NAUSEA

Just a word as to toxic impurities relative to after-sickness. This phenomenon is from a practical standpoint the great disadvantage of ordinary ether anaesthesia.

In an earlier paper I drew attention to a poisonous gas, X derived by the superheating of ether, when in contact with a metal. A few weeks ago I was enabled to analyze it, and found it to be made up of aldehyde, carbon-dioxide, ethylene, carbon-monoxide and others. As all ether is superheated to a more or less degree, in soldering of the cans, there is a possibility of carbon-monoxide being present. In very small traces it will cause nausea and in an air dilution of less than '15 per cent. it has caused death according to Dixon. Ether on being heated in a closed cylinder at 100°C. for one hour, will, on administration, produce excessive nausea. It is not known whether in this case there is a carbon-monoxide relation, for the research along this line has not been completed, on account of technical difficulties.

There is still another factor in after-sickness, and that is the narcotic group. Most people who take alcohol know that if they become very drunk they are going to suffer from after-sickness, and alcohol is a narcotic. Therefore it follows, that if in a certain sample of ether there is not a sufficient quantity of ethylene (or CO<sub>2</sub>) we will, in order to induce analgesia, have to give an overdose of the narcotic solvents and post narcotic sickness must follow.

Before closing I wish to emphasize that this is only a preliminary paper and hardly an introduction to the different fields of research on anaesthesia which have been opened up.

#### DEMONSTRATION

June 14th, 1917.

Royal Victoria Hospital, Montreal.

Surgeons:

Dr. Archibald,

Dr. Garrow,

Colonel Keenan.

8.45 a.m.

Case 1.

Cat: Age 9 months.

Administered sixty drops of ether (absolute) (saturated with ethylene). Time—two and a half minutes; cat relieved of all sensation, yet capable of walking.

8.55 a.m.

Case 2.

Chinaman: Middle-aged.

Anæsthetic: Absolute ether, carbon-dioxide.

Induction to analgesia three and a half minutes.

Operation: Infected upper arm. Eight incisions were made over biceps. Patient free from sensation but not at all unconscious.

Operation time: Ten minutes.

9.10 a.m.

Case 3.

Cat: Same animal as before.

Administered three ounces absolute ether. Animal became hyperæsthetic. Slightest touch would make it yell. Then a struggling stage started with shortness of breath and expiratory meouw. A further half-ounce caused a short gaspy respiration but no analgesia.

9.20 a.m.

Case 4.

Englishman: Middle-aged.

Anæsthetic: Absolute ether—ethylene.

Induction to analgesia—four minutes.

Operation: Resection splintered bone from elbow. Patient capable of carrying on active conversation and yet was entirely free from sensation.

Time of operation: Fifteen minutes.

#### CONCLUSIONS

1. Absolute gas-free ethyl-ether is not an anæsthetic.

2. It acts only:

(a) As a vehicle for analgesic gases:

Carbon-dioxide

Ethylene

Other gases

(b) As a narcotic stimulant.



3. Other narcotics occurring in commercial ether, and acting similar to ethyl ether, are:

Di-methyl-ether	}	Only in ethers/made from methylated alcohols.
Methyl-ethyl ether		
Methyl-propyl ether		
Alcohol		
4. Ether, on being sufficiently superheated in contact with a metal gives rise to carbon-monoxide and other gases.
5. After-sickness from commercial ether administration, for surgery, may be from:
  - (a) Narcotic poisoning (excessive administration of narcotic solvents).
  - (b) Carbon-monoxide poisoning.
  - (c) Surgical shock.
6. Irritating substances occurring in commercial ether are:
  - (a) Alcohols and acetones, causing anterior nasal irritation.
  - (b) Aldehydes, causing naso pharyngeal and bronchial irritation.
  - (c) Organic acids, producing bad odours.
7. Respiration rate is in part a factor in early analgesia.